about 90% identity to the amino acid sequence shown at positions 29 through 256, inclusive, of Figures 4A-4C (SEQ ID NO:2)[; and

(b) control elements that are operably linked to said nucleic acid molecule whereby said coding sequence can be transcribed and translated in a host cell, and at least one of said control elements is heterologous to said coding sequence].

II. REMARKS

Claims 1-12 are presently pending in this application. Claims 1-12 stand variously rejected under 35 U.S.C. §§ 112, 102 and 103. These rejections are believed to be overcome by the above amendments and are otherwise traversed for reasons discussed below.

Overview of the Above Amendments

Claims 1-6 have been amended to claim the subject invention with greater particularity and in order to respond to rejections under 35 U.S.C. §112, second paragraph. Specifically, claim 1 incorporates the subject matter from existing claims 2 and 3 into a Markush group. Additionally, the term "comprising" has been replaced with the recitation "consisting of" in the claim. Claim 1 further specifies that the immunogenic fragment of the recited sequences comprises "at least about 10 contiguous amino acids" from the specified sequence.

Claims 2 and 3 have been amended to delete the terminology "substantially homologous and functionally equivalent," objected to by the Office under 35 U.S.C. §112, second paragraph. The claims now specify that the CAMP factor polypeptide has "at least about 90% identity" to the specified amino acid sequence of SEQ ID NO:2.

Claim 4 has been rewritten in independent format to incorporate the recitations present in previous claim 1-3 in a Markush group and to specify the length of the

immunogenic fragment. Claims 5 and 6 have been amended to recite specific members of the Markush group present in claim 4 and to depend therefrom.

Support for these amendments can be found in the claims as filed, as well as throughout the specification at, e.g., page 13, line 24; and page 16, lines 19-22. Thus, no new matter has been added to the application by way of the foregoing amendments. A copy of the currently pending claims, incorporating the amendments made herein, is appended for the Examiner's convenience.

35 U.S.C. § 112, Second Paragraph

Claims 2-3 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. In particular, The Office stated that applicants had failed to recite a specific sequence identification number in claims 2 and 3. However, sequence identification numbers were indeed added to the claims in the Preliminary Amendment which accompanied the Sequence Listing, filed February 18, 1999. Clarification is therefore requested.

The Office also objected to the terminology "substantially homologous" and "functionally equivalent." The Office asserts: "The term substantially homologous in the claims is a relative term which renders the claim indefinite, in the absence of a clear recitation of the specific algorithm and specific parameters employed for comparison of the sequences." Office Action, page 3. The Office further argues that the term "functionally equivalent" has "no clearly defined meaning as applied to an amino acid sequence." Office Action, page 3.

Although applicants do not agree with the Office's assertions, applicants have eliminated these terms from the claims. The claims now recite instead that the CAMP factor polypeptide has "at least about 90% identity" to the specified amino acid sequence of SEQ ID NO:2. Applicants, at page 16, lines 5-11 of the specification, explain that two

programs such as ALIGN. Further, applicants note the present Office Action issued prior to the Patent Office's new directive with respect to % identity language. In particular, as explained by Group Director John Doll at the October, 1999 AIPLA meeting in Crystal City, the USPTO policy towards claims reciting percent identity has now changed and such claims will no longer be rejected under 35 U.S.C. §112, second paragraph.

Based on the foregoing, applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 2-3, 5-6, 8-9, and 11-12 stand rejected under 35 U.S.C. § 112, first paragraph. The Office alleges that the specification does not recite the specific algorithm and parameters used to determine homology. However, as explained above, the claims now recite that the CAMP factor polypeptide has "at least about 90% identity" to the specified amino acid sequence of SEQ ID NO:2 and it is applicants' understanding that such terminology is no longer being challenged by the Office under 35 U.S.C. §112. Thus, this basis for rejection has been overcome.

Additionally, the Office asserts:

> The specification fails to provide characteristics of any polypeptide variants of the SEQ ID NO:2 which function as a *Streptococcus uberis* CAMP factor polypeptide equivalent to the disclosed SEQ ID NO:2. The specification fails to teach the biological functionally equivalent of the protein. One skilled in the art would have reason to doubt the alleged function of the protein because the art teaches that polypeptide isolated based on percent homology do not predictably display the functions of their homologs...The specification fails to teach what are the critical protein portions that are needed for the *Streptococcus uberis* CAMP factor activity...The art specifically teaches that even a single amino acid change is a protein leads to unpredictable change in the biological activity of the protein...Moreover, no assay for Streptococcus uberis CAMP factor homolog function is set forth in the specification which could allow one skilled in the art to screen for functionally equivalent variants

Office Action, pages 4-5. However, applicants submit that the Office's view reflects a basic misunderstanding of applicants' invention.

In particular, the invention is directed to nucleic acid molecules which encode "immunogenic" *Streptococcus uberis* polypeptides. Applicants are not, however, interested in providing nucleic acid molecules that encode a "biologically active" CAMP factor i.e., one displaying CAMP cytolytic activity. Indeed, such cytolytic activity is toxic and undesirable. Thus, the Office's concern with preserving the biological activity of the CAMP factor is in error.

Rather, applicants' concern is only with providing nucleic acid molecules that encode immunogenic (e.g., epitope-containing) *S. uberis* CAMP factor polypeptides. Epitopes contained within the immunogenic polypeptides need not be conformational, as evidenced by the fact that the CAMP factor polypeptide used in the examples does not retain its native conformation since it has been denatured and no refolding step is employed prior to use. Applicants submit, therefore, that one of skill in the art would not find it unduly burdensome to identify immunogenic polypeptides containing linear epitopes. In fact, techniques for doing so are discussed in the patent application at page 13, lines 10-20. Applicants therein explain that immunogenic CAMP factor polypeptides can be rapidly and readily identified using, e.g., techniques described in issued U.S. Patent No. 4,708,871. The method detailed in the '871 patent involves concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. These methods can easily be used to identify immunogenic polypeptides derived from the *S. uberis* CAMP factor protein without undue experimentation. The Office is reminded that even a large amount of experimentation is permitted under §112, first paragraph, provided it is routine. *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. App. 1982) (a claim is acceptable under §112 even if it

Furthermore, 35 U.S.C. §112, first paragraph does not require that specific examples be present in order to satisfy the enablement requirement. In fact, how an enabling teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of §112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)).

Furthermore, there is no requirement that applicants present data pertaining to each and every embodiment covered in a broad claim. Indeed, the CCPA in *In re Angstadt*, 190 USPQ 214 (CCPA 1976), cautions against such a burdensome requirement:

> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with 'thousands' of examples or the disclosure of 'thousands' of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid 'literal' infringement of such claims by merely finding another analogous catalyst complex which could be used in 'forming hydroperoxides'. (Emphasis in original.)

Id. at 218.

Applicants submit that they have indeed complied with the enablement requirement of 35 U.S.C. §112, first paragraph. Routine methods for mapping epitopes were known to those of skill in the art at the time the application was filed and are taught in the specification. Applicants submit that, given the level of skill in the art, the

practice the claimed invention without undue experimentation. Applicants have therefore met their duty under 35 U.S.C. §112, first paragraph and respectfully request withdrawal of this rejection.

35 U.S.C. § 102

Claims 1-3 are rejected under 102(b) as allegedly anticipated by Williams et al., *Lett Appl Microbiol* (1991) 12:23-8 ("Williams"). The Office alleges that Williams teaches "isolated chromosomal DNA from *Streptococcus uberis* which inherently comprises the coding sequence encoding *Streptococcus uberis* CAMP factor." Office Action, page 6. However, applicants respectfully submit that their claims distinguish over Williams.

In particular, applicants' claims pertain to isolated nucleic acid molecules "consisting of" coding sequences for immunogenic *Streptococcus uberis* CAMP factors. Accordingly, claims 1-3 do not read on chromosomal DNA, or restriction digests as described in Williams. Thus, this basis for rejection has been overcome. Withdrawal thereof is respectfully requested.

Claims 1-3 were also rejected under 102(b) as allegedly anticipated by Podblielski, *Med Microbiol Immunol* (1994) 183:239-256 ("Podblielski"). The Office argues that Podblielski teaches an isolated nucleic acid molecule of the cf6 gene encoding a group B Streptococcus CAMP factor comprising a coding sequence that encodes an amino acid sequence for an immunogenic *Streptococcus uberis* CAMP factor with 63.5% identity and with 10 epitopes "identical to SEQ ID NO:2." The Office also argues that "the art teaches that an immunogenic fragment (an immunogenic epitope) is approximately equivalent to 5 amino acids." The Office bases this argument on a purported SPTREMBL search, the results of which were supposed to have accompanied the Office Action. However, no such search was included with the Action. Accordingly,

applicants are unable to fully address this rejection and request that the Office provide the search results.

Nevertheless, in an effort to hasten prosecution, applicants have amended the claims to recite that the sequences have "at least about 90% identity" to the specified amino acid sequence of SEQ ID NO:2. Further, the immunogenic fragments are characterized as including at least 10 contiguous amino acids from the sequence of SEQ ID NO:2. Thus, the claims are not anticipated by Podblielski and withdrawal of this basis for rejection is respectfully requested.

Rejections Under 35 U.S.C.§ 103(a)

Claims 1-12 stand rejected as allegedly unpatentable over Podblielski as applied to claims 1-3, and Sambrook et al., *Molecular Cloning, A Laboratory Manual* Chapter 17, Expression of Cloned Genes in *Escherichia coli* ("Sambrook").

The Office argues:

> Podblielski teaches a cloned nucleic acid molecule comprising a coding sequence that encodes an amino acid sequence for an immunogenic *Streptococcus uberis* CAMP factor and substantially homologous and functionally equivalent to the amino acid sequence shown in Figures 4A-4C or an immunogenic fragment thereof.

Office Action, page 8. The Office acknowledges that Podblielski fails to teach "inserting the cloned gene into an expression vector" but argues that Sambrook teaches standard methods for expression of cloned genes. Thus, the Office asserts it would have been obvious "to insert the cloned gene of Podblielski into a recombinant vector comprising a heterologous control element that can be operably linked to the cloned sequence..." Office Action, pages 8-9. However, applicants disagree with this contention.

First of all, Podblielski's sequences are all derived from either of *Streptococcus* [illegible] and not *S. uberis*. In fact, *S. uberis* is not even

sequences having at least about 90% identity to those specified in SEQ ID NO:2, or immunogenic fragments of at least 10 contiguous amino acids therefrom. Podblielski does not disclose or suggest such sequences or cloning such sequences. Sambrook fails to provide the missing link in that Sambrook pertains generally to the field of gene expression, does not in anyway pertain to *S. uberis*, let alone *S. uberis* CAMP factor, and therefore does not further elucidate nucleic acid molecules encoding immunogenic CAMP factor polypeptides as claimed. Prior to applicants' invention, no one had cloned and expressed CAMP factor proteins from *S. uberis*. Accordingly, applicants submit that the Office has failed to present a prima facie case of obviousness and that this basis for rejection should be withdrawn.

III. CONCLUSION

Applicants respectfully submit that the claims are novel and nonobvious over the art and comply with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

If the Examiner notes any further matters which he believes may be expedited by a telephone interview, he is requested to contact the undersigned attorney at (650) 325-7812.

Respectfully submitted,

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